REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Postharvest diseases are often extensions of disease occurring in the field or orchard. Brown rot of stone fruits (*Monilinia fructicola* (Wint.) Honey), for example, may cause blossom and twig blighting in the orchard. Infections in the orchard may not be visible at harvest if fruits are not refrigerated. *Colletotrichum gloeosporioiders* (Penz.) Arx may attack blossoms or leaves and young fruit of citrus, avocados, mangos, papayas, and a wide range of other tropical and subtropical species; infections in developing fruit are usually latent, and rot lesions appear only at the onset of fruit ripening. *Pezicula malicorticis* (Jacks.) Nannfld. causes cankers of limbs of apples and pears; infections in developing fruit are latent, and active rotting usually commences only after the fruit has spent several months in storage and proceeds during -1°C storage because the organism is able to grow at very low temperatures. These fungi used as examples are able to penetrate the cuticle and epidermis of the fruit.

Whether capable of being penetrated directly or not, wounds are often the usual means by which the fungus enters fruit. Cuts, punctures, bruises, and abrasions cannot be avoided completely during harvest and handling. If the cuticle and epidermis are broken, spores find nutrients and humidity in fresh wounds ideal for spore germination and colonization. Separation of fruits from the parent plant at harvest creates an unavoidable wound that encourages stem-end rots.

Rots developing at the blossom end usually involve prior colonization of floral parts. For example, *Botrytis* blossom-end rot (*B. cinerea*) sometimes occurs in Bartlett pears after a month or two in storage at -1°C. Initiation of rot in fruit flesh is associated with old styles and stamens retained within the fruit. Floral infections occur in the senescing floral parts at the end of blossoming. Mostly these floral parts are invaded by *Alternaria* spp. and common saprophytic fungi, but *B. cinerea* also is found occasionally. Not all fruits having *B.cinerea*-invaded floral parts rot in storage, but a significant percentage do. By contrast, test fruits remain free from *Botrytis* blossom-end rot if the old floral parts of developing fruits are free from *B. cinerea*. Rotting of fruits in storage is greatly reduced by a single orchard spray with a fungicide at the end of blossoming.

Contact infection, by which mycelia grow from a rotting fruit to contact and penetrate nearby fruit, is an especially serious aspect of some very common postharvest pathogens. The ever-enlarging "nest" of rotting fruit tied together by fungus mycelia will involve all fruit in a container, if given sufficient time.

Disease or threat of disease dictates in large measure the manner in which perishable fruits are handled. In recent decades, fruits have been shipped to increasingly greater distances from points of production. Exploitation of these distant markets, however, may offer large economic benefits only if the life of the commodity is stretched to its limit. Diseases and disorders ordinarily manageable during handling and transcontinental transit and marketing may be excessive when transoceanic marine transport of longer duration is involved. Similarly, the extension of marketing periods by storing fruits until they near the end of their physiological life may cause additional disease problems. Losses are especially serious if they occur in market areas, because the costs of sorting, packaging, cooling, storage, and transportation, which may greatly exceed production costs, have already been incurred. Of even greater long-term importance may be an impaired reputation leading to reduced future sales.

Postharvest diseases of fruit cause 15 to 25% losses yearly in the fruit industry worldwide and much of this is due to rot caused by microorganisms. Fungicides, which have been the primary means of controlling postharvest diseases, have come under scrutiny as posing potential oncogenic risks when applied to processed foods. Thus, research efforts have been intensified to develop biological control procedures for postharvest diseases of fruits and vegetables that pose less risk to human health and the environment.

Considerable attention has been placed on assessing the use of antagonistic microorganisms as a viable alternative to the use of synthetic fungicides. Two basic approaches are available for using antagonistic microorganisms to control postharvest diseases. Naturally occurring antagonists that already exist on fruit and vegetable surfaces have been shown to control several rot pathogens on diverse commodities. Alternatively, artificially introduced antagonists have been shown to be effective in biologically controlling postharvest pathogens.

Since 1983, an explosion of research has occurred in the area of biological control of postharvest diseases by artificially introduced antagonists, mostly on fruit diseases. For example, rot on apples was controlled with yeast, while brown rot in apricots was controlled with *Bacillus subtilis*. Mold incidence was reduced from 35% to 8% in lemon peel

by a species of *Trichoderma*. Biocontrol of citrus rot pathogens was demonstrated with *Bacillus subtilis*. Such antagonists have various modes of action: antibiosis or competition for nutrients and space or both, induction of resistance in the host tissue, and direct interaction with the pathogen.

While treatment with antagonistic bacterial or fungal species may be, at least to some extent, effective in controlling postharvest diseases, there are a number of factors which must be considered before this approach is used in commercial applications. First, the antagonists must be grown and maintained for use in treatments. This may result in significant expense and regulatory burdens depending on when and how frequently such antagonists would be applied. Also, it is questionable whether growers would want to maintain bioreactors for growing and propagating particular antagonist strains. Second, the efficacy of those antagonists may depend on storage conditions during shipment of harvested fruit. Some antagonists may not be able to tolerate variations in conditions during shipment, thereby allowing the pathogens to overcome any inhibitory effects of the antagonists. Given the above problems, it is not surprising that few of the antagonists reported to control plant pathogens have been successfully transferred from the laboratory into the field or postharvest environment.

Thus, there still exists a need to provide an effective, commercially viable method for treating fruits and vegetables to control postharvest diseases which avoids entirely or otherwise significantly reduces the need for fungicide treatments. In particular, it would be desirable to provide an effective, practicable treatment which presents little or no harm to humans or the environment.

The present invention is directed to overcoming these and other deficiencies in the art.

In response to the restriction requirement, applicants hereby confirm the election of Group I (i.e., claims 1-20 and 43-46). Non-elected claims 21-42 and 47-50 have been canceled without prejudice to them being pursued in a divisional application.

The October 24, 2002, office action states that "[t]he preliminary amendment (A) has been entered" (see page 3 of Paper No. 8). Applicants respectfully submit that no preliminary amendment has been filed in this case, and further request that the U.S. Patent and Trademark Office ("PTO") confirm the state of the record in regard to this matter.

The rejection of claims 1-20 and 43-46 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 5,776,889 to Wei et al. ("Wei") in view of Fajardo et al., "Differential Induction of Proteins in Orange Flavedo by Biologically Based Elicitors and Challenged by *Penicillium digitatum* Sacc.," Biological Control 13:143-151 (1998) ("Fajardo") is respectfully traversed.

Wei teaches a method of imparting pathogen resistance to plants through topical application of an isolated hypersensitive response elicitor protein or polypeptide derived from a fungal and/or bacterial plant pathogen.

Fajardo teaches the use of various biologically based non-proteinaceous inducing agents for delaying the onset and progression of green mold of oranges, an important postharvest disease of citrus. Specifically, Fajardo teaches the use of chitosan, Margosan-O®, Aspire®, and combinations thereof, for postharvest treatment of the oranges. (Contrary to the interpretation by the PTO set forth at page of the outstanding office action (Paper No. 8), Fajardo does not teach application of 'elicitor proteins.' As noted above and explained below, none of the inducing agents of Fajardo is proteinaceous.)

A proper *prima facie* showing of obviousness requires the PTO to satisfy three requirements. First, the prior art relied upon, coupled with knowledge generally available to one of ordinary skill in the art, must contain some suggestion which would have motivated the skilled artisan to combine the references. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the PTO must show that, at the time the invention was made, the proposed modification had a reasonable expectation of success. See Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Finally, the combination of references must teach or suggest each and every limitation of the claimed invention. See In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Application of these standards to the present invention demonstrates that the PTO has failed to establish a *prima facie* case of obviousness for several reasons.

Firstly, applicants submit that the PTO has failed to establish that motivation exists to combine the teachings of Wei and Fajardo. The PTO asserts in the outstanding office action that one of ordinary skill in the art would have been motivated to use isolated hypersensitive response elicitor proteins or polypeptides of the type taught by Wei for use in inhibiting crop disease "given the importance of HR elicitors applicants to plants or plant parts, especially fruits, in preventing postharvest diseases, at storage and during transport as taught by Fajardo" (see pages 5-6 of Paper No. 8).

As noted above, Wei involves the use of hypersensitive response elicitor proteins or polypeptides, albeit for use of imparting pathogen resistance to plants treated therewith. In contrast, Fajardo is limited to the three above-listed non-proteinaceous inducing agents (either alone or in combination), none of which is even remotely similar to the hypersensitive response elicitor proteins or polypeptides of Wei or of the present invention. Contrary to the suggestion by the PTO, none of the inducing agents applied by Fajardo is even an elicitor <u>protein</u>. Chitosan is a poly-D-glucosamine derived from the chitin in crustacean exoskeletons (see Exhibit A attached hereto), Margosan-O® includes as the active ingredient azadirachtin, a terpenoid extracted from neem seed (see Exhibit B attached hereto), and Aspire® includes as the active ingredient a strain of *Candida oleophila*, a yeast that has been investigated for the control of postharvest pathogens (see Exhibit C attached hereto). Fajardo suggests that chitosan and Margosan-O® are directly toxic to *Penicillium digitatum* (Fajardo at page 148, second column), while Aspire® is a microbial competitor (<u>Id.</u>). In addition, although Fajardo refers to the inducing agents as 'elicitors', those inducing agents are <u>nowhere</u> described as being capable of inducing a hypersensitive response and, hence, are not hypersensitive response elicitor proteins or polypeptides. Thus, unlike the hypersensitive response elicitor proteins or polypeptides used by Wei, none of Fajardo's inducing agents is a protein or polypeptide, is capable of eliciting a hypersensitive response, or is derived from a plant pathogenic fungus or bacterium.

Because the inducing agents utilized by Fajardo belong to distinctly different classes of products as compared to the hypersensitive response elicitor proteins or polypeptides of Wei and because those inducing agents operate by distinctly different mechanisms as compared to the hypersensitive response elicitor proteins or polypeptides of Wei, one of ordinary skill in the art would not have been motivated to combine the teachings of Wei and Fajardo.

Secondly, even if, assuming *arguendo*, there were some suggestion of combining the teachings of Wei and Fajardo (which there is none), there has been no showing by the PTO of a reasonable expectation of success in achieving the presently claimed invention. As noted above, Wei teaches the topical application of hypersensitive response elicitor proteins or polypeptides to plants in order to impart plant pathogen resistance to those plants. Nowhere does Wei suggest or provide any expectation that the <u>postharvest</u> application of the hypersensitive response elicitor proteins or polypeptides to harvested fruits or vegetables would impart disease resistance to those treated fruits or vegetables. The PTO

has cited none. On the other hand, given the distinct differences between the non-proteinaceous inducing agents employed by Fajardo and the hypersensitive response elicitor protein or polypeptides of Wei, the results of Fajardo are limited to the non-proteinaceous inducing agents disclosed therein (see Fajardo at page 144, col. 1). Fajardo cannot provide any expectation of success in using the hypersensitive response elicitor proteins or polypeptides disclosed in Wei. Thus, there is no showing that, at the time of the invention, one of ordinary skill in the art would have reasonably expected that postharvest application of the hypersensitive response elicitor proteins or polypeptides of Wei to fruits or vegetables would have been successful in inhibiting postharvest disease or desiccation, or for enhancing longevity of the fruit or vegetable ripeness.

Further, Wei provides no basis to expect that disease resistance, induced in plants treated with a hypersensitive response elicitor protein or polypeptide, can be transferred to fruits or vegetables subsequently removed from the plant, affording disease or desiccation resistance in the harvested fruit or vegetable and enhancing longevity of the fruit or vegetable ripeness. The PTO has cited none. Fajardo is completely silent with respect to preharvest application of the non-proteinaceous inducing agents disclosed therein. Thus, there is likewise no showing that, at the time of the invention, one of ordinary skill in the art would have reasonably expected that preharvest application of the hypersensitive response elicitor proteins or polypeptides of Wei to plants (or fruits or vegetables on the plants) would have been successful in inhibiting postharvest disease or desiccation of fruits or vegetables removed (i.e., harvested) from the treated plants, or for enhancing longevity of the fruit or vegetable ripeness.

Finally, neither Wei nor Fajardo make any mention that the respective treatments described therein can enhance the longevity of fruit or vegetable ripeness. The PTO certainly has not cited to any such teaching or suggestion. Therefore, even if, assuming *arguendo*, there were some suggestion of combining the teachings of Wei and Fajardo (which there is none), the combination of Wei and Fajardo both fails to provide any expectation that the longevity of fruit or vegetable ripeness can be enhanced and fails to teach or suggest each and every element of claims 43-46.

For the above reasons, applicants respectfully submit that claims 1-20 and 43-46 are allowable over Wei and Fajardo and that the rejection thereof under 35 U.S.C. § 103(a) should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Date 1/22/03 | Wendy L. Barry